Reduced functional connectivity induced by longitudinal alterations of structure and perfusion may be associated with cognitive impairment in patients on maintenance hemodialysis

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Abstract

Background: Hemodialysis (HD) leads to cognitive impairment; however, the pathophysiology of maintenance HD remains unclear. This study aimed to investigate the longitudinal alterations in gray matter volume (GMV) and cerebral blood flow (CBF) in patients on follow-up HD compared with baseline HD, examine the alterations in functional connectivity (FC) by defining co-changed brain regions as seed points, and investigate the correlation between the co-changed brain regions and neuropsychological test scores. Methods: Twenty-seven patients with HD and 30 healthy controls were enrolled in this study. All participants underwent high-resolution T1-weighted imaging, arterial spin labeling, and functional MR imaging to measure GMV, CBF, and FC. The patients on HD were assessed at baseline and 3 years subsequently. Results: The right and left medial superior frontal gyrus (SFGmed.L) exhibited significantly lower GMV and CBF in patients on follow-up HD compared with patients on baseline HD and lower FC between the SFGmed.L and left middle temporal gyrus (MTG.L). Decreased FC between the SFGmed.L and MTG.L was positively correlated with neuropsychological test scores in the follow-up HD group. Conclusions: Reduced GMV and CBF may result in decreased FC between the SFGmed.L and MTG.L, which may be associated with cognitive impairment in patients on maintenance HD. Our findings provide unique insights into the pathological mechanisms of patients on maintenance HD with cognitive impairment.

Introduction

The prevalence of chronic kidney disease (CKD) has increased over the past few decades, and CKD has become a serious public health problem worldwide (Ene-Iordache et al., 2016; G. B. D. Chronic Kidney Disease Collaboration, 2020). When the glomerular filtration rate is < 15 ml/min/1.73 m^2, CKD progresses to end-stage renal disease (ESRD) (Foley and Collins, 2007). Hemodialysis (HD) is the most common kidney replacement therapy for patients with ESRD (Romagnani et al., 2017), but it leads to a range of complications, including cognitive impairment (Drew et al., 2019), cerebral atrophy (Wang et al., 2020), cerebrovascular diseases (Jin et al., 2020a), iron deposition (Wang et al., 2020a), white matter lesions (Chou et al., 2019), and restless legs syndrome (Wang et al., 2021). Cognitive impairment is extremely common in patients on HD, with a prevalence of 80% (Murray et al., 2006; van Zwieten et al., 2018). However, the pathophysiology of cognitive impairment in patients on HD remains unclear. Accordingly, cognitive function may experience abnormal brain changes, such as atrophic cerebral gray matter, abnormal cerebral blood flow (CBF), changes in brain activity, and iron deposition. Therefore, identifying the changes of patients on HD in gray matter volume (GMV), CBF, and functional connectivity (FC) may help understand neuronal mechanisms in patients with HD.

Multimodal magnetic resonance imaging (MRI) techniques, such as voxel-based morphological (VBM) analysis (Jin et al., 2020b; Zhang et al., 2013), arterial spin labeling (ASL) (Findlay et al., 2019; Jiang et al., 2016), resting-state functional MRI (rs-fMRI) (Chen et al., 2015; Jin et al., 2021), diffusion tensor imaging (Zhang et al., 2015), and quantitative susceptibility mapping (Chai et al., 2015; Hao Wang et al., 2022), play a critical role in the early diagnosis of cognitive impairment in patients on HD. Patients on HD exhibit abnormal brain changes using these techniques. VBM studies have shown that patients on HD have lower GMV in some brain regions compared with healthy controls (HCs). For example, Qiu et al. found a significant decrease in GMV in the bilateral medial orbito-prefrontal, bilateral dorsal lateral prefrontal, and left middle temporal cortices in patients on HD (Qiu et al., 2014). Moreover, Jin et al. reported a significant decrease in GMV in the bilateral rectus, caudate, and temporal gyrus in patients on HD (Jin et al., 2020b). In a recent ASL study, Jiang et al. found that patients on HD had lower CBF mainly in the bilateral frontal and anterior cingulate cortices compared with patients with ESRD who were not on dialysis (Jiang et al., 2016). Using rs-fMRI, previous investigators have observed abnormal brain FC in the default mode network (DMN) of patients on HD (Zheng et al., 2023). As these studies are cross-sectional, it is impossible to not consider the influence of individual factors on their results. Therefore, further longitudinal studies are required to determine the long-term consequences of HD on brain changes and whether these changes correlate with cognitive impairment. We hypothesized that long-term HD may lead to changes in GMV, CBF, and FC in patients on HD.

In the current study, we aimed to (1) clarify the longitudinal variations of GMV and CBF in patients on HD, (2) define co-changed brain regions as seed points and illustrate abnormal seed-based FC in patients on HD, and (3) investigate the correlation between the co-changed brain regions and neuropsychological test scores.

Methods

All the participants were right-handed and had ESRD caused by glomerulonephritis or primary hypertensive nephropathy. All the participants underwent dialysis thrice a week for > 6 months, and each HD session lasted for approximately 4 h. The exclusion criteria were as follows: (I) participants aged < 18 years; (II) participants who received other renal replacement therapies; (III) participants with a history of diabetic nephropathy; (IV) participants with a history of brain lesions, including stroke, head trauma, hemorrhage, infarction, and tumors; (V) participants with a history of psychiatric disorders; (VI) participants with a history of alcohol abuse or drug use; and (VII) participants with a history of claustrophobia. This study was approved by the Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University. All participants provided informed consent, in accordance with the principles of the Declaration of Helsinki.

Sixty-three patients were recruited into the HD group. Each patient underwent brain MRI assessment, laboratory examinations, and Montreal Cognitive Assessment (MoCA) evaluation at baseline, and most of the patients (34 of 63) underwent a second examination (brain MRI assessment, laboratory examinations, and MoCA evaluation) after 3 years. However, seven patients (7 of 34) were excluded because of unqualified image quality and head motion. Ultimately, 27 patients who met the inclusion criteria were enrolled in the HD follow-up group. Thirty HCs were recruited from local communities. Laboratory examinations and MoCA evaluation were not performed in the HC group. No follow-up examinations were performed in the HC group. The details of the participants are presented in Supplementary 1. The demographic data, laboratory examinations, and neurophysiological tests of all participants are presented in Table 1.

Magnetic resonance imaging data acquisition

A 3.0 Tesla magnetic resonance system (Discovery MR750W, General Electric, Milwaukee, Wisconsin, USA) with an eight-channel phased array coil was used to capture images. Before MRI, all participants were instructed to avoid ingesting any meals or beverages containing caffeine.

The three-dimensional (3D) brain volume imaging sequence was used to acquire a structural image with the following parameters: repetition time (TR) = 8.8 ms, echo time (TE) = 3.5 ms, inversion time = 450 ms, axial slices = 196, slice thickness = 1 mm, matrix = 256×256, field of view (FOV) = 240×240 mm^2, and

flip angle (FA) = 15°.

The pseudo-continuous ASL imaging sequence was applied for perfusion imaging with the following parameters: TR = 4844 ms, TE = 10.5 ms, FOV = 240 × 240 mm^2, axial slices = 36, slice thickness = 4 mm, matrix = 128 × 128, labeling time = 2025 ms, post-label delay = 2025 ms, excitations = 3, and spiral-in readout = 512 sample points with 8 arms. The CBF maps were extracted from the original ASL data using an MRI scanner.

The fMRI maps were collected using the following parameters: TR = 2000 ms, TE = 35 ms, axial slices = 28, slice thickness = 5 mm, time points = 200, matrix = 64 × 64, FOV = 24 × 24 cm^2, and FA = 90°.

VBM data processing

The Digital Imaging and Communications in Medicine format of the MRI T1 raw image data acquired by the 3D-BRAVO sequence was converted to the Neuroimaging Informatics Technology Initiative (NIfTI) format. Subsequently, all attempted images were assessed for quality layer by layer, and images with large artifacts were rejected. VBM data processing was performed using the MATLAB-based (R2018b; MathWorks) Statistical Parametric Mapping software (SPM12) and the SPM12-based standard pipeline of a computational anatomy toolbox (CAT12). First, the T1-weighted images were normalized to Montreal Neurological Institute (MNI) space using the Diffeomorphic Anatomical Registration Through the Exponentiated Lie (DARTEL) algebra (Ashburner, 2007) to enable the analysis of group data. After normalizing the T1-weighted images, tissue probability maps were used to segment gray matter, white matter, and cerebrospinal fluid tissues. Finally, the GMV images were further smoothed to reduce spatial noise using a 6 mm × 6 mm × 6-mm full-width half maximum (FWHM) isotropic Gaussian kernel. The details are presented in step 1 of Figure 1.

ASL data processing

After subtracting the labeled images from the control images, we generated ASL difference images using a single-compartment model. Ultimately, the proton density-weighted reference and ASL difference images produced the CBF images. The CBF maps were converted to NIfTI format images, all the attempted images were assessed for quality layer by layer, and images with large artifacts were rejected. Using the DARTEL technique of the SPM12 software, the CBF maps in the individual spaces of all participants were individually normalized to the MNI standard space. After normalization, the quality of the CBF images of all participants was assessed again, and severely distorted CBF images were removed for the next step of analysis. All data were standardized using the mean division method of the Data Processing Assistant for Resting-State fMRI (DPARSF) advanced edition software package (Yan et al., 2016) to increase parameter sensitivity. Finally, all standardized CBF images were spatially smoothed using an isotropic Gaussian kernel with a 6 mm × 6 mm × 6-mm FWHM to improve the signal-to-noise ratio of the CBF images. The details are presented in step 2 of Figure 1.

Functional connectivity processing

The DPARSF Advanced Edition software package was used to preprocess the functional imaging data. The first 10 volumes for each participant were excluded from the acquisition of 200 volumes. We corrected 190 volumes for temporal differences between the slices. After slice time correction had been made, head motion was corrected by realignment, and participants with head motion > 3.0 mm were excluded. A nuisance regression analysis was performed with the motion parameters from the Friston-24 model, the white matter, cerebral spinal fluid, and global signals as covariates. A co-registration step was then performed between the individual T1 and mean functional images. The acquired T1 images were then segmented and spatially normalized to the MNI space using the DARTEL algebra technique. The normalized functional images were filtered using a bandpass filter with a frequency range of 0.01–0.10 Hz. Significantly different regions based on changes in GMV and CBF were further selected as seed points for FC analyses. Therefore, we defined the left medial superior frontal gyrus (SFGmed.L) and right medial superior frontal gyrus (SFGmed.R) as seed points for subsequent FC analysis. FC maps were derived from the correlation between the mean time series

of the seed points and the time series of the voxels within the total brain cortices. Fisher's Z transformation was used to ensure that the data were normally distributed. Spatial smoothing was performed on the FC maps with a 6 mm × 6 mm × 6-mm FWHM isotropic Gaussian kernel. The details are presented in step 3 of Figure 1.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., IBM Company, Chicago, IL, United States) and the SPM12 package were used for data analysis. Statistical significance was defined as $P < 0.05$. The Shapiro–Wilk test was used to determine whether the data were normally distributed. Two independent sample t-tests were used to assess the differences in age and total intracranial volume (TIV) between the HD (including baseline and follow-up HD) and HC groups. Fisher's exact test was used to determine differences in sex between the HD and HC groups. A paired-samples t-test was used to demonstrate differences in systolic pressure and hemoglobin, calcium, phosphorus, parathyroid hormone, and serum ferritin levels between the baseline and follow-up HD groups. The paired-samples Wilcoxon test was used to demonstrate differences in diastolic pressure, creatinine levels, and MoCA scores between the baseline and follow-up HD groups.

A paired sample t-test was performed to determine the differences in GMV, CBF, and FC between the follow-up and baseline HD groups using SPM12. Two independent sample t-tests were performed using SPM12 with age, sex, and TIV as covariates to determine the differences in GMV, CBF, and FC between the follow-up and baseline HD and HC groups. When GMV and CBF were compared between the groups, multiple comparisons were corrected using a voxel-wise threshold of $P < 0.001$ and a cluster-level false discovery rate (FDR) threshold of $P < 0.05$. When FC was compared between groups, multiple comparisons were corrected using a voxel-wise threshold of $P < 0.001$ and a cluster-level Gaussian random field (GRF) threshold of $P < 0.05$. To examine the relationship between MoCA scores and GMV, CBF, and FC, Pearson's correlation analysis was used for the baseline and follow-up HD groups.

Results

Demographics and clinical characteristics

Table 1 shows the characteristic demographic data of the participants. Age, TIV, and sex did not differ significantly between the two groups ($P > 0.05$). There were significant differences in diastolic pressure, calcium levels, and parathyroid hormone levels between the follow-up and baseline HD groups ($P = 0.026$, 0.004, and 0.001, respectively). Compared with the baseline HD group, the MoCA scores of the follow-up HD group were significantly lower ($P < 0.001$).

GMV differences among the groups

A comparison of GMV differences among the groups is shown in Figure 2 and Supplementary 2. Compared with the baseline HD group, the follow-up HD group exhibited lower GMV in the bilateral medial superior frontal gyrus (SFGmed) and bilateral dorsolateral superior frontal gyrus (SFGdor) ($P < 0.05$, cluster-level FDR-corrected).

Compared with the HC group, the baseline HD group exhibited lower GMV in the bilateral SFGmed, bilateral rectus, bilateral putamen, bilateral anterior cingulate, and bilateral anterior cingulate and paracingulate gyri (ACG) ($P < 0.05$, cluster-level FDR-corrected). Compared with the HC group, the baseline HD group exhibited higher GMV in the bilateral thalamus ($P < 0.05$, cluster-level FDR-corrected).

Compared with the HC group, the follow-up HD group exhibited lower GMV in the bilateral SFGmed, bilateral SFGdor, and bilateral median cingulate and paracingulate gyri (DCG), left middle frontal gyrus (MFG), and left putamen ($P < 0.05$, cluster-level FDR-corrected). Compared with the HC group, the follow-up HD group exhibited higher GMV in the left thalamus ($P < 0.05$, cluster-level FDR-corrected).

CBF differences among the groups

A comparison of the differences in CBF between the groups is shown in Figure 3 and Supplementary 3. Compared with the baseline HD group, the follow-up HD group exhibited lower CBF in the bilateral SFGmed, bilateral SFGdor, bilateral middle temporal gyrus (MTG), and left MFG ($P < 0.05$, cluster-level FDR-corrected).

Compared with the HC group, the baseline HD group exhibited lower CBF in the right insula ($P < 0.05$, cluster-level FDR-corrected). Compared with the HC group, the baseline HD group exhibited higher CBF in the right thalamus and SFGmed.R ($P < 0.05$, cluster-level FDR-corrected).

Compared with the HC group, the follow-up HD group exhibited lower CBF in the bilateral SFGmed and right MTG ($P < 0.05$, cluster-level FDR-corrected). Compared with the HC group, the HD group exhibited higher CBF in the bilateral thalamus ($P < 0.05$, cluster-level FDR-corrected).

FC differences among the groups

As part of the present study, the SFGmed.L and SFGmed.R were selected as seed regions for FC analyses. The results for seed point SFGmed.L are presented in Figure 4(A) and Supplementary 4. Compared with the baseline HD group, the follow-up HD group exhibited lower FC with the left MFG (MTG.L), left parahippocampal gyrus (PHG), and left posterior cingulate gyrus (PCC) ($P < 0.05$, cluster-level GRF-corrected). Compared with the HC group, the baseline HD group exhibited lower FC with the MTG.L ($P < 0.05$, cluster-level GRF-corrected). Compared with the HC group, the follow-up HD group exhibited lower FC with the MTG.L, bilateral PCC, and left hippocampus ($P < 0.05$, cluster-level GRF-corrected).

The results for the seed point SFGmed.R are presented in Figure 4(B) and Supplementary 5. Compared with the baseline HD group, the follow-up HD group exhibited lower FC with the MTG.L and right PHG ($P < 0.05$, cluster-level GRF-corrected). Compared with the HC group, the baseline HD group exhibited lower FC with the MTG.L and right PCC ($P < 0.05$, cluster-level GRF-corrected). Compared with the HC group, the follow-up HD group exhibited lower FC with the MTG.L, right PCC, right PHG, and right hippocampus ($P < 0.05$, cluster-level GRF-corrected).

Correlations between MoCA scores and GMV, CBF, and FC in the baseline and follow-up HD groups

The decreased GMV in the SFGmed.L was positively correlated with the MoCA scores in the baseline HD group ($r = 0.411$, $P = 0.033$). The decreased FC between the SFGmed.L and MTG.L was positively correlated with the MoCA scores in the follow-up HD group ($r = 0.4468$, $P = 0.014$). Correlation analyses based on the GMV of the SFG.L in the follow-up HD group showed no significant correlation. Correlation analyses based on the FC of the SFG.L in the baseline HD group showed no significant correlation. Correlation analyses based on the CBF of the SFG.L showed no significant correlation. A series of correlation analyses based on SFGmed.R revealed no significant correlation. The results of the correlation analysis based on SFGmed.L are shown in Figure 5.

Discussion

We observed that the patients on baseline HD showed significantly lower GMV compared with HCs, and some brain regions in the patients on follow-up HD showed significantly lower GMV compared with the patients on baseline HD, specifically in the bilateral SFGmed and SFGdor. The patients on baseline HD showed more subtle abnormalities in CBF compared with HCs, but some brain regions in the patients on follow-up HD showed significantly lower CBF, including the bilateral SFGmed, bilateral SFGdor, and bilateral MTG. The patients on follow-up HD showed decreased FC between the bilateral SFGmed and MTG.L compared with the patients on baseline HD.

HD, the most common kidney replacement therapy, can cause brain atrophy. In our study, the patients on baseline HD demonstrated an extensively lower GMV compared with HCs. In addition, some brain regions in the patients on follow-up HD showed significantly lower GMV compared with the patients on baseline HD, specifically in the bilateral SFGmed and bilateral SFGdor. We observed a reduction in GMV in the bilateral rectus of patients on HD at baseline, which is consistent with the findings of previous studies.

Jin et al.[13] demonstrated that the GMV of the bilateral rectus, caudate, and temporal gyri decreased in patients on HD. Compared with the patients on baseline HD, the patients on follow-up HD had lower GMV in the bilateral SFGmed and bilateral SFGdor, which is similar but not identical to the results of previous studies. For example, Wang et al. investigated the longitudinal changes in GMV in patients on HD and found regionally lower GMV in the bilateral frontal lobes, bilateral insula, bilateral temporal lobes, bilateral rolandic operculum, and bilateral caudate in the patients on follow-up HD compared with the patients on baseline HD (Huiying Wang et al., 2022). However, the patient duration in our study was longer than that reported in a previous study. In our study, the bilateral SFGmed, SFGdor, and insula were located in the prefrontal cortex (PFC). In the human brain, the PFC is responsible for regulating cognitive progress at the highest level (Yan and Rein, 2022). Moreover, it plays an essential role in cognitive functions, including working memory, attention, and decision-making (Carlén, 2017). In particular, there is a strong correlation between the SFGmed and the cognitive function (Li et al., 2013; Liu et al., 2022). According to our study, the decrease in GMV in the PFC is in line with that observed in previous studies, indicating that HD may exacerbate deficits in executive function of patients with ESRD. This may be a neurological mechanism for patients on HD with cognitive impairment.

HD can also result in abnormal cerebral perfusion. In the present study, we examined both cross-sectional and longitudinal variations in CBF. In our study, the baseline HD group showed a more subtle alteration in CBF compared with the HC group. However, the follow-up group showed a significantly lower CBF in the PFC compared with the baseline HD group and higher CBF in the bilateral thalamus compared with the HC group. This suggests that HD, as an independent factor, is highly likely to adversely affect CBF. Similar but not identical findings have been reported in other studies in patients on HD. For example, Liu et al. found that patients on HD had lower CBF than patients on baseline HD in the orbitofrontal cortex and hippocampus after 6 months (Li et al., 2020). In the present study, the regions of longitudinally decreased CBF are also located in the PFC. A close relationship exists between changes in the brain volume and CBF (Dai et al., 2009; Prohovnik et al., 2007). In patients on HD, PFC atrophy and reduced CBF may explain to some extent the cause of their cognitive impairments.

Alterations in CBF and GMV may have contributed to abnormal brain activity in patients on HD. In our study, compared with the baseline HD group, the follow-up HD group exhibited significantly lower FC between the SFGmed.L with the left PCG, left MTG, and left PHG, exhibiting significantly decreased FC between the SFGmed.R, bilateral MTG, and right PHG. Interestingly, these regions are mostly located within the DMN. In other words, HD may disrupt FC within the DMN through a potential mechanism. Using the independent component analysis technique, Ni et al. found that patients with ESRD had lower FC in the DMN compared with HCs, specifically in the PCC, precuneus, and PFC. There is some similarity between the results of our cross-sectional study and those of the study (Ni et al., 2014); however, the differences may be associated with the differences in technology and grouping. We found that the patients on baseline HD had lower FC compared with HCs between the SFGmed.L with the left MTG and left PHG and between the SFGmed.R with the left MTG and right PCC, suggesting that patients at baseline already have reduced FC within the DMN (Buckner et al., 2008). Furthermore, HD may exacerbate this trend by disrupting neuronal connections in functional networks. In the present study, impaired FC was found in the prefrontal-PCC circuits of patients on HD, revealing a gradual decrease in FC in the SFGmed from controls to baseline patients to follow-up patients with PCC, which is a critical region responsible for higher-order cognitive control (Ries et al., 2006; Sheth et al., 2012). The reduced FC between the SFGmed and PHG in patients suggests that the fronto-limbic network is hypoconnected. In general, the PHG is involved in episodic memory, including associative memory, source memory, and memory retrieval (Aminoff et al., 2013). According to a meta-analysis of functional imaging studies on semantic processing, the SFGmed, MTG, and PCC are brain regions that are reliably activated by general semantic processes (Binder et al., 2009; Binder and Desai, 2011). In this study, we hypothesized that reduced FC between the bilateral SFGmed and MTG.L may reflect a decline in semantic processing function. Our findings provide unique insights into the pathological mechanisms of patients on HD with cognitive impairment.

Structural damage may lead to functional damage in patients on HD. At baseline, the decreased GMV in

the SFGmed.L was positively associated with MoCA scores, indicating that cognitive impairment is likely to be the predominant structural impairment in patients on baseline HD. After 3 years, the decreased FC between the SFGmed.L and MTG.L was positively correlated with MoCA scores, suggesting that functional damage becomes a more dominant factor resulting in cognitive impairment.

Our study has some limitations. First, the different HD durations between the patients may have influenced the results. Hence, further studies are required to determine how the HD duration affects brain changes and cognitive impairment in patients on HD. Second, the effects of different ESRD pathologies on the results were not considered. In the future, we will explore the possible influences of various pathological types. Third, this study had a small sample size. Therefore, additional studies with larger sample sizes of patients with ESRD on HD should be conducted.

Conclusion

HD may cause changes in the GMV and CBF of patients on maintenance HD. Reduced GMV and CBF may result in decreased FC between the SFGmed.L and MTG.L, which may be associated with cognitive impairment in patients on maintenance HD. Our findings provide unique insights into the pathological mechanisms of patients on maintenance HD with cognitive impairment.

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Disclosure

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Table

Table 1. Demographics and neuropsychologic tests of the baseline HD, follow-up HD, and HC group

	Baseline HD (n = 27)	Follow-up HD (n = 27)	HC (n = 30)	*P*-value
Age (years)	54.2±9.3	57.1±9.3	52.9±8.0	0.578[a+] 0.067[a++]
TIV(cm^3)	1447.2±125.7	1443.6±133.9	1478.3±133.9	0.372[a+] 0.326[a++]
Sex (male/female)	15/12	15/12	15/15	0.792[b]
HD duration (months)	91.6±66.1	123.4±65.7	NA	NA
SP (mmHg)	141.6±24.6	136.0±22.6	NA	0.258[c]
DP (mmHg)	77 (67, 93)	71 (62,80)	NA	0.026[d]
Hemoglobin (g/L)	116.9±11.5	115.8±10.4	NA	0.654[c]
Creatinine (μmol/L)	901.0 (861.9, 1102.2)	1034.2 (873.3, 1121.1)	NA	0.248[d]
Calcium (mmol/L)	2.2±0.2	2.3±0.1	NA	0.004[c]
Phosphorus (mmol/L)	1.9±0.5	1.8±0.6	NA	0.469[c]
PTH (pg/mL)	212.6±147.5	299.4±232.4	NA	0.001[c]
Serum ferritin (ng/mL)	196.8±122.6	169.2±114.8	NA	0.314[c]
MoCA	20.44±3.32	18.00±2.35	NA	¡0.001[c]

HD, hemodialysis; HC, healthy control; TIV, total intracranial volume; SP, Systolic pressure; DP, Diastolic pressure; PTH, Parathyroid hormone; NA, not applicable; MoCA, Montreal Cognitive Assessment.

[+]Comparison between the baseline HD and HC group

[++]Comparison between the follow-up HD and HC group

[a] Two independent sample t-test

[b] Fisher's exact test

[c] Paired-samples t-test

[d] Paired-samples Wilcoxon test

Figure legends

Figure 1 Flowchart of the experimental procedure. GMV, gray matter volume; CBF, cerebral blood flow; FC, functional connectivity; MoCA, Montreal Cognitive Assessment.

Figure 2 GMV alterations among the baseline HD, follow-up HD, and HC groups. The cold color indicates a significant decrease in GMV between groups ($P < 0.05$, FDR-corrected). The hot color indicates a significant increase in GMV between groups ($P < 0.05$, FDR-corrected).

SFGmed.L, left superior frontal gyrus, medial; SFGmed.R, right superior frontal gyrus, medial; THA.L, left thalamus; THA.R, right thalamus; HD, hemodialysis; HC, healthy control; GMV, gray matter volume; FDR, false discovery rate.

Figure 3 CBF alterations among the baseline HD, follow-up HD, and HC groups. The cold color indicates a significant decrease in CBF between groups ($P < 0.05$, FDR-corrected). The hot color indicates a significant increase in CBF between groups ($P < 0.05$, FDR-corrected).

SFGmed.L, left superior frontal gyrus, medial; SFGmed.R, right superior frontal gyrus, medial; THA.R, right thalamus; HD, hemodialysis; HC, healthy control; CBF, cerebral blood flow; FDR, false discovery rate.

Figure 4 A Difference among groups in FC between the SFGmed.L and the rest of the whole brain. The cold color indicates a significant decrease in FC between groups ($P < 0.05$, GRF-corrected). The hot color indicates a significant increase in CBF between groups ($P < 0.05$, GRF-corrected). **B** Difference among groups in FC between the SFGmed.R and the rest of the whole brain. The cold color indicates a significant decrease in FC between groups ($P < 0.05$, GRF-corrected). The hot color indicates a significant increase in CBF between groups ($P < 0.05$, GRF-corrected).

MTG.L, left middle temporal gyrus; PHG.L, left parahippocampal gyrus; PHG.R, right parahippocampal gyrus; PCG.L, left posterior cingulate gyrus; PCG.R, right posterior cingulate gyrus; SFGmed.L, left superior frontal gyrus, medial; SFGmed.R, right superior frontal gyrus, medial; HD, hemodialysis; HC, healthy control; FC, functional connectivity; GRF, Gaussian random field.

Figure 5 A Correlation between MoCA scores and decreased GMV in the SFGmed.L in the baseline HD group ($r = 0.411$, $P = 0.033$). **B** Correlation between MoCA scores and decreased GMV in the SFGmed.L in the follow-up HD group ($r = 0.350$, $P = 0.073$). **C** Correlation between MoCA scores and decreased CBF in the SFGmed.L in the baseline HD group ($r = 0.044$, $P = 0.827$). **D** Correlation between MoCA scores and decreased CBF in the SFGmed.L in the follow-up HD group ($r = –0.060$, $P = 0.765$). **E** Correlation between MoCA scores and decreased FC in the SFGmed.L-MTG.L in the baseline HD group ($r = 0.245$, $P = 0.217$). **F** Correlation between MoCA scores and decreased FC in the SFGmed.L-MTG.L in the follow-up HD group ($r = 0.447$, $P = 0.014$).

GMV, gray matter volume; CBF, cerebral blood flow; FC, functional connectivity; MoCA, Montreal Cognitive Assessment; HD, hemodialysis; HC, healthy control; SFGmed.L, left superior frontal gyrus, medial; MTG.L, left middle temporal gyrus.

Supplementary 1 Summary of the baseline HD, follow-up HD, and HC group inclusions and exclusions. HD, hemodialysis; HC, healthy control; MoCA, Montreal Cognitive Assessment.